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(54) Title: USE OF C5A RECEPTOR ANTAGONIST IN THE TREATMENT OF FIBROSIS

(57) Abstract: This invention relates to the use of an antagonist of a G protein-coupled receptor in the prevention and/or treatment of fibrosis, such as the treatment of fibrosis associated with myocardial infarction or diabetes or certain pulmonary conditions. In a preferred embodiment the antagonist is a C5a receptor antagonist, more preferably a cyclic peptide antagonist of the C5a receptor. In particular the invention provides a method of prevention, treatment or alleviation of a fibrotic condition, comprising the step of administering an effective amount of an antagonist of a G protein-coupled receptor to a subject in need of such treatment.

CLAIMS

1. A method of prevention, treatment or alleviation of a fibrotic condition, comprising the step of administering an effective amount of an antagonist of a G protein-coupled receptor to a subject in need of such treatment.

2. A method according to claim 1, in which the antagonist is a C5a receptor antagonist.

3. A method according to claim 1 or claim 2, in which the antagonist is a peptide or a peptidometic compound.

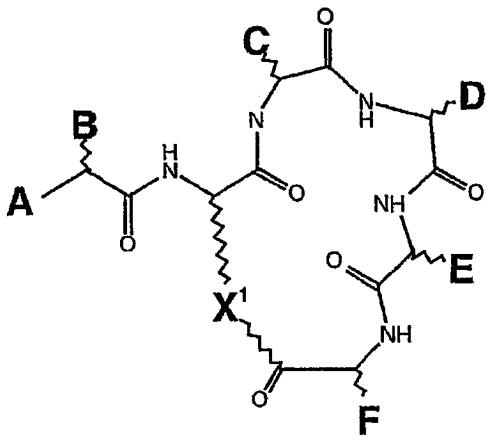
4. A method according to claim 3, in which the antagonist is a cyclic peptide or a cyclic peptidometic compound.

5. A method according to any one of claims 1 to 3, in which the antagonist

(a) is an antagonist of a G protein-coupled receptor,

(b) has substantially no agonist activity, and

(c) is a cyclic peptide or peptidomimetic compound of formula I



where A is H, alkyl, aryl, NH_2, NH-alkyl,

$N(alkyl)_2$, NH-aryl, NH-acyl, NH-benzoy, $NHSO_3$, $NHSO_2$-alkyl, $NHSO_2$-aryl, OH, O-alkyl, or O-aryl;

B is an alkyl, aryl, phenyl, benzyl, naphthyl or indole group, or the side chain of a D- or L-amino acid such as L-phenylalanine or L-phenylglycine, but is not the side chain of glycine, D-phenylalanine, L-homophenylalanine, L-tryptophan, L-homotryptophan, L-tyrosine, or L-homotyrosine;

C is a small substituent, such as the side chain of a D-, L- or homo-amino acid such as glycine, alanine, leucine, valine, proline, hydroxyproline, or thioproline, but is preferably not a bulky substituent such as isoleucine, phenylalanine, or cyclohexylalanine;

D is the side chain of a neutral D-amino acid such as D-Leucine, D-homoleucine, D-cyclohexylalanine, D-homocyclohexylalanine, D-valine, D-norleucine, D-homo-norleucine, D-phenylalanine, D-tetrahydroisoquinoline, D-glutamine, D-glutamate, or D-tyrosine, but is preferably not a small substituent such as the side chain of glycine or D-alanine, a bulky planar side chain such as D-tryptophan, or a bulky charged side chain such as D-arginine or D-Lysine;

E is a bulky substituent, such as the side chain of an amino acid selected from the group consisting of L-phenylalanine, L-tryptophan and L-homotryptophan, or is L-1-napthyl or L-3-benzothienyl alanine, but is not the side chain of D-tryptophan, L-N-methyltryptophan, L-homophenylalanine, L-2-naphthyl L-tetrahydroisoquinoline, L-cyclohexylalanine, D-leucine, L-fluorenylalanine, or L-histidine;

F is the side chain of L-arginine, L-homoarginine, L-citrulline, or L-canavanine, or a bioisostere thereof, ie. a side chain in which the terminal guanidine or urea group is retained, but the carbon backbone is replaced by a group which has different structure but is such that the side chain as a whole reacts with the target protein in the

same way as the parent group; and

X is $-(CH_2)_nNH-$ or $(CH_2)_n-S-$, where n is an integer of from 1 to 4, preferably 2 or 3; $-(CH_2)_2O-$; $-(CH_2)_3O-$; $-(CH_2)_3-$; $-(CH_2)_4-$; $-CH_2COCHRNH-$; or $-CH_2-CHCOCHRNH-$, where R is the side chain of any common or uncommon amino acid.

6. A method according to claim 5, in which A is an acetamide group, an aminomethyl group, or a substituted or unsubstituted sulphonamide group.

7. A method according to claim 6, in which A is a substituted sulphonamide, and the substituent is an alkyl chain of 1 to 6, preferably 1 to 4 carbon atoms, or a phenyl or toluyl group.

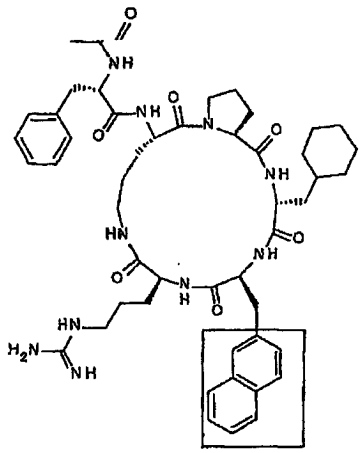
8. A method according to any one of claims 1 to 6, in which the antagonist is a C5a receptor antagonist which has antagonist activity against C5aR, and has no C5a agonist activity.

9. A method according to any one of claims 1 to 7, in which the compound has a receptor affinity IC50<25μM, and an antagonist potency IC50<1μM.

10. A method according to any one of claims 1 to 8, in which the compound is selected from the group consisting of compounds **1** to **6**, **10** to **15**, **17**, **19**, **20**, **22**, **25**, **26**, **28**, **30**, **31**, **33** to **37**, **39** to **45**, **47** to **50**, **52** to **58** and **60** to **70** described in International patent application No.PCT/AU02/01427.

11. A method according to claim 10, in which the compound is PMX53 (compound **1**), compound **33**, compound **60** or compound **45**.

12. A method according to claim 10, in which the compound is PMX53, having the formula



13. The use of a C5a receptor antagonist for the manufacture of a medicament for use in the treatment of a fibrotic condition.